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DRUG EFFICACY

The Effect of Treatment Expectation on Drug Efficacy: Imaging the Analgesic Benefit of the Opioid Remifentanil

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Evidence from behavioral and self-reported data suggests that the patients' beliefs and expectations can shape both therapeutic and adverse effects of any given drug. We investigated how divergent expectancies alter the analgesic efficacy of a potent opioid in healthy volunteers by using brain imaging. The effect of a fixed concentration of the μ-opioid agonist remifentanil on constant heat pain was assessed under three experimental conditions using a within-subject design: with no expectation of analgesia, with expectancy of a positive analgesic effect, and with negative expectancy of analgesia (that is, expectation of hyperalgesia or exacerbation of pain). We used functional magnetic resonance imaging to record brain activity to corroborate the effects of expectations on the analgesic efficacy of the opioid and to elucidate the underlying neural mechanisms. Positive treatment expectancy substantially enhanced (doubled) the analgesic benefit of remifentanil. In contrast, negative treatment expectancy abolished remifentanil analgesia. These subjective effects were substantiated by significant changes in the neural activity in brain regions involved with the coding of pain intensity. The positive expectancy effects were associated with activity in the endogenous pain modulatory system, and the negative expectancy effects with activity in the hippocampus. On the basis of subjective and objective evidence, we contend that an individual's expectation of a drug's effect critically influences its therapeutic efficacy and that regulatory brain mechanisms differ as a function of expectancy. We propose that it may be necessary to integrate patients' beliefs and expectations into drug treatment regimes alongside traditional considerations in order to optimize treatment outcomes.

INTRODUCTION

Pharmacological treatments rely on predictable physiological effects that are determined by their biological properties. However, it has been a longstanding clinical notion that an individual's beliefs and expectations can significantly influence the therapeutic benefit and adverse effects of a pharmacological treatment. This suggests that any drug treatment inevitably comprises physiological and psychological components (*1*). However, in clinical settings, the interplay of physiological and psychological treatment effects is often neglected or seen as a nuisance variable that needs to be controlled for, as in placebo-controlled randomized trials. Experimental studies have addressed positive and negative psychological treatment effects in terms of placebo and nocebo responses (*2*). Placebo and nocebo responses represent positive and negative medical responses, respectively, after the administration of an inert substance or sham treatment. These are triggered by psychosocial variables forming the treatment context, such as expectation of treatment outcome via verbal cues, previous experience, or patient-physician interactions (*3*).

Placebo analgesia represents the best-studied placebo response (*4*) and is mediated by an activation of the opioid-dependent endogenous pain modulatory system (*5*–*7*). Nocebo effects, including nocebo hyperalgesia, are less well investigated but have also been associated with an interference with the endogenous opioid system (*8*). The effects of positive or negative expectation of the effectiveness of the treatment may therefore be mediated by the same biological systems through which drugs exert their treatment effects.

However, placebo and nocebo experiments have been performed with biologically inert compounds, the use of which in daily clinical practice is constrained by ethical and legal limitations (*9*). Knowledge regarding the effect of psychological factors on the efficacy of active pharmacological treatments is surprisingly sparse. Furthermore, there is scant information about the neural mechanisms by which the effects of expectations interact with the pharmacological effects of biologically active drugs. However, behavioral observations from studies that compared the open and hidden application of drugs or explicitly modulated the expectancy regarding a given drug by verbal instruction show that psychological treatment effects can influence drug efficacy (*10*–*17*).

The power of negative expectations has been demonstrated by Dworkin *et al.* (*16*), who showed a reversal of analgesia by nitrous oxide in dental pulp pain when the participants expected the drug to increase awareness of bodily sensations. A limitation of those studies is that these observations cannot rule out that the observed effects result from a bias in patients' reported information (for example, due to social desirability), rather than from a direct neurobiological interaction of psychological and physiological effects.

Here, we investigated the neural mechanisms by which the psychological state modulates the efficacy of a potent analgesic pharmacological treatment. Specifically, we investigated how positive and negative expectancies of treatment outcome affect the analgesic effect of the μ-opioid receptor agonist remifentanil. Within the large and distributed network of brain areas that respond to painful stimuli, several regions, such as the thalamus, the posterior insula, the midcingulate

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cortex (MCC), and the primary somatosensory cortex, have been consistently shown to be correlated with the intensity of nociceptive inputs and resultant pain perception (*18*, *19*). Activity levels in these brain regions can therefore serve as a surrogate marker of analgesia. Functional magnetic resonance imaging (fMRI) was used (i) as an objective index of analgesia by tracking pain-related brain responses in typical pain intensity coding areas during different expectation conditions and (ii) to characterize the brain mechanisms underlying the influence of positive and negative expectations on drug efficacy. We hypothesized that the individuals' expectancies of the effectiveness of the drug would modify subjective as well as objective indicators of the analgesic effect of remifentanil.

We used a model of experimental heat pain in healthy participants where the neurobiological mechanisms of pain perception, analgesia, and expectancy are well known (*18*, *20*). The analgesic effect of a fixed 0.8 ng/ml effect site concentration (estimated concentration within the brain) was studied under three different conditions: without expectation of analgesia, with expectancy of a positive analgesic effect, and with negative expectancy of analgesia [that is, expectation of hyperalgesia (exacerbation of pain)].

Remifentanil is a potent synthetic μ-opioid agonist with a rapid onset of action, a context-sensitive half-life of 3 to 4 min (*21*), and an elimination half-life of ~10 min (*22*). These properties make it ideal for healthy volunteer experimental studies where rapid onset and offset of opioid action is required. Positive and negative expectations of the efficacy of remifentanil were induced by verbal instruction and reinforced in a conditioning-like procedure before the main experiment. We used fMRI to validate that the subjects' expectancy effects of drug efficacy, as assessed by the behavioral report, were reflected in core brain areas of pain processing. fMRI was thereby used to test for reporting bias and to help elucidate the neural mechanisms underpinning the effects of expectancy on treatment efficacy.

RESULTS

Results refer to the main experimental session performed with fMRI and are based on the 22 healthy volunteers who completed the study, comprising two study visits (for details, see Materials and Methods).

Behavioral results

Using visual analog scales (VASs), we assessed the analgesic efficacy of the potent μ-agonist remifentanil under the three different expectancies of treatment outcome by pain intensity ratings and pain unpleasantness ratings (Fig. 1).

Pain intensity ratings. Repeated-measures analysis of variance (ANOVA) revealed a significant effect for experimental condition ($F_{3,63}$ = 42.6, P < 0.001). Post hoc tests showed that the hidden application of remifentanil without treatment expectancy significantly reduced pain intensity ratings from 66 ± 2 during baseline saline infusion to 55 ± 3 [$t(21)$ = 5.1, P < 0.001].

Positive expectancy significantly enhanced analgesia, as pain ratings further decreased to 39 ± 3 [$t(21)$ = 6.4, P < 0.001]. Negative expectancy, when the subjects had been led to believe that the drug was stopped, resulted in a considerable increase in pain intensity from 39 ± 3 (positive expectancy run) to 64 ± 3 (negative expectancy run) [$t(21)$ = 8.5, P < 0.001]. Negative expectancy fully negated the intrinsic analgesic effect of remifentanil, as pain intensity under negative expectancy did not differ from pain intensity during baseline saline infusion [$t(21)$ = 0.68, P = 0.5] (Fig. 1).

Unpleasantness ratings. Pain unpleasantness ratings showed a similar pattern. The ANOVA revealed significant differences among the four conditions ($F_{3,63}$ = 28.8, P < 0.001). Post hoc tests showed that unpleasantness ratings decreased from baseline (saline) to the hidden application of remifentanil without treatment expectation from 52 ± 4 to 38 ± 4 [$t(21)$ = 5.2, P < 0.001], further decreased when remifentanil was given with positive expectancy from 38 to 23 ± 3 [$t(21)$ = 4.9, P < 0.001], and increased in the fourth run, when remifentanil was given with a negative treatment expectancy from 23 to 47 ± 5 [$t(21)$ = 5.3, P < 0.001]. The negative expectation in this fourth run fully negated the analgesic effect of remifentanil, because unpleasantness ratings under negative expectancy did not differ from baseline (Fig. 1).

Anxiety ratings. For technical reasons, the anxiety ratings are available only from 19 of 22 participants. Repeated-measures ANOVA showed a main effect of experimental condition on the anxiety ratings

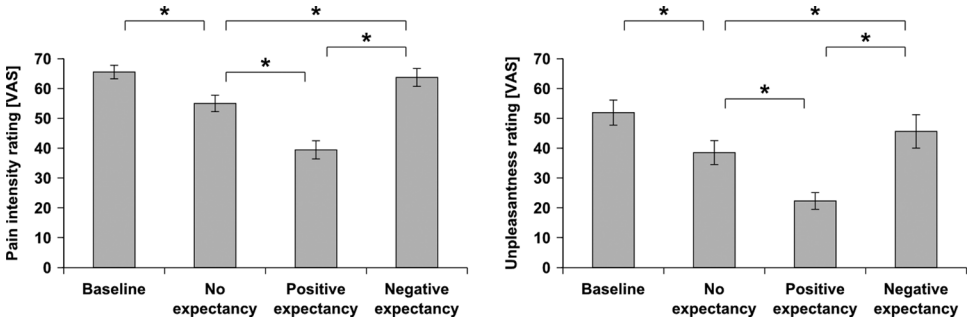

Fig. 1. Behavioral effects of the contextual modulation of opioid analgesia. (Left) Pain intensity ratings obtained on the VAS (0 to 100) for the four experimental runs. (Right) Pain unpleasantness ratings obtained at the end of each of the four experimental runs show the same context-dependent pattern. Error bars indicate SEM. *P < 0.05.

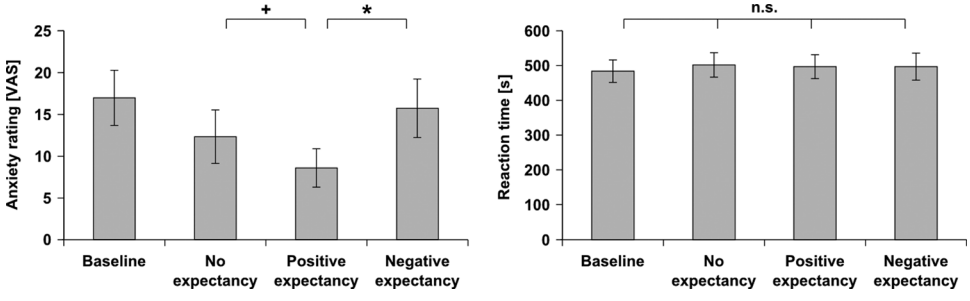

Fig. 2. Behavioral effects of the expectancy modulation of opioid analgesia. (Left) Anxiety ratings obtained on the VAS (0 to 100) at the beginning of each of the four experimental conditions. (Right) Mean reactions times (seconds) in the reaction time task performed at the beginning of each trial. Error bars indicate SEM. *P < 0.05; ^{+}P = 0.05. n.s., not significant.

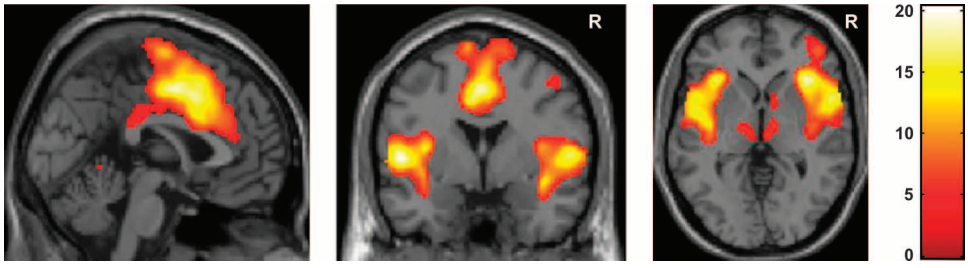

Fig. 3. Brain activation to painful stimulation. BOLD responses to painful heat stimulation in the first run (saline application) only. For a complete list of brain areas, see table S1. The images are thresholded at $P < 0.05$ corrected. Color bar indicates t score.

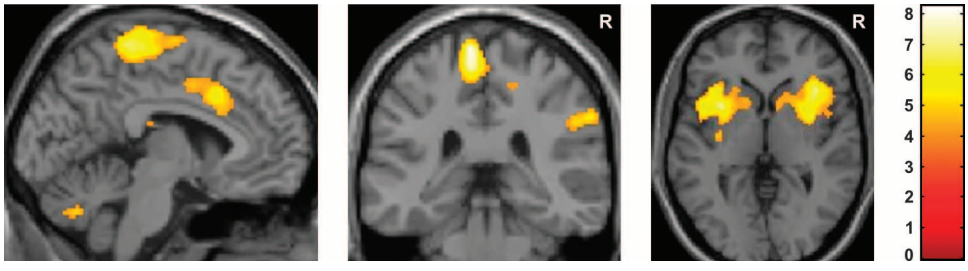

Fig. 4. Brain correlates of the intrinsic effect of opioid analgesia. BOLD activations to painful heat stimulation that are greater during baseline than during covert administration of remifentanil (for details, see table S2). The images are thresholded at $P < 0.05$ corrected. Color bar indicates t score.

Table 1. Brain areas displaying opioid analgesia and its expectancy-dependent modulation. Pain-related BOLD responses that track the pain intensity ratings in the four experimental conditions (using z-transformed mean ratings from all four experimental runs as contrast weights). Coordinates are denoted by x, y, z in millimeters according to the Montreal Neurological Institute (MNI) space, and strength of activation is expressed in t scores (df = 63). All Ps < 0.05 corrected (*), using small volume correction (SVC) as indicated in Supplementary Methods, or 0.001 uncorrected. ACC, anterior cingulate cortex; MCC, midcingulate cortex; PAG, periaqueductal gray; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; R, right; L, left.

Region	Coordinate of peak voxel		Voxel level (T)
	R	L	R/L
S1		−8, −40, 72	/6.3*
S2	56, −26, 26	−52, −28, 26	3.6/3.8*
ACC	6, 20, 36	−6, 16, 34	5.6*/5.8*
MCC	4, −2, 44		5.2*/
Insula	36, 8, 6	−32, 6, 10	/6.0*
Thalamus		−16, −20, 8	/4.6*
Putamen	24, 6, −8	−24, 4, 0	3.9*/3.8*
Cerebellum	30, −50, −32		4.6/
PAG		−4, −28, −2	/3.3*
Amygdala		−18, −2, −16	/3.4*
Hippocampus		−34, −12, −12	/3.6*

obtained at the beginning of each run ($F_{3,51} = 4.8, P < 0.01$). Post hoc t tests revealed that this effect was mainly driven by a reduced anxiety with positive expectancy from 12 ± 3 to 9 ± 2 [$t(18) = 2.4$, $P = 0.05$] and a substantial increase in anxiety with negative expectancy from 9 ± 2 to 16 ± 3 [$t(18) = 3.2$, $P < 0.05$] (Fig. 2).

The analgesic benefit from positive expectancy was negatively correlated with anxiety ratings obtained at the start of the respective run ($r = -0.55$, $P < 0.01$), indicating that participants who were less anxious showed a greater analgesic benefit of positive expectancy.

These expectancy-dependent changes in opioid analgesia as measured by pain intensity and anxiety ratings are not the result of sensitization/habituation processes or confounding effects of prolonged opioid infusion (for example, opioid tolerance). This was confirmed by the two control experiments (see Supplementary Methods and Results and figs. S4 and S5) and supported by the posthoc analysis of the time course of changes in analgesia during the different expectancy conditions (see Supplementary Results and fig. S6).

Reaction times. There was no significant main effect of experimental condition on reaction times ($F_{3,63} = 0.58$, $P = 0.6$). Consistent with opioid sedation, reaction times were slightly slower during the hidden infusion run compared to the baseline; however, this difference was not significant, going from 485 ± 32 to 503 ± 35 ms [$t(21) = 1.5$, $P = 0.21$] (Fig. 2).

fMRI results

We first determined brain areas responsive to painful thermal stimulation. The results show that the painful stimuli significantly activated the well-known cerebral pain network (*19*) including the primary and secondary somatosensory cortices (S1 and S2), the insula, and the MCC. Subcortical responses were recorded in the thalamus, basal ganglia, brainstem, and cerebellum (table S1 and Fig. 3). The intrinsic effect of remifentanil resulted in a significant reduction of pain-related BOLD (blood oxygen level–dependent) responses in all of these brain regions (baseline run > no-expectancy run). The most pronounced effects were observed in S1, the anterior cingulate cortex (ACC), the insula, and the striatum (for details, see table S2 and Fig. 4).

We then tested whether the observed placebo and nocebo changes in analgesia (indicated by the changes in perceived pain intensity) would be reflected in levels of activation of pain and opioid-sensitive brain networks.

If these changes were seen, these results would support the conclusion that the expectancy-dependent differences in reported analgesia are not the result of reporting bias or socially desirable responding. Therefore, we tested for pain-related BOLD responses that change with the subjective pain intensity ratings in the different experimental conditions—baseline, without expectation, with positive expectation, and with negative expec-

tation of analgesia (using *z*-transformed mean ratings from all four experimental runs as contrast weights). Indeed, changes in pain intensity during the different conditions were reflected in changes in activation in the core areas of the cerebral pain network including S1 (corresponding to the expected somatotopic representation of the lower leg), S2, MCC, insula, basal ganglia, contralateral thalamus, and brainstem, including the periaqueductal gray (PAG) (Table 1 and Fig. 5; see also Supplementary Methods and Results and fig. S2).

Given the clinical relevance of expectation within the therapeutic context, we were particularly interested in the opposing effects of positive and negative expectancy on the brain circuitry subserving opioid analgesia. Therefore, we compared brain responses to identical pain stimuli under conditions of negative and positive expectancy. We chose to contrast these two conditions where both expectancy and drug are present, but only the direction of expectancy (positive or negative) is manipulated. The results show that the attenuated analgesic effect (that is, increase in pain intensity) during negative expectancy was reflected by an increase in brain activity in the cerebral pain network including the S1, MCC, insula, and thalamus. In addition, we observed increases in brain activity in the hippocampus bordering the amygdala, medial prefrontal cortex, and the cerebellum (Table 2 and Fig. 6). An additional simple regression analysis revealed that the increase in neural activity in the hippocampus, MCC, and medial prefrontal cortex predicts the individual increase in perceived pain intensity. These brain areas are thus likely to be involved in the effects of negative expectancy on opioid analgesia.

Finally, we aimed to identify brain regions that mediated the increased analgesic potency of opioids during positive expectancy. We therefore determined brain areas that showed increased activation when remifentanil was given under conditions of positive expectancy compared to negative expectancy. This response pattern was observed in the dorsolateral prefrontal cortex, ACC (including rostral and perigenual/subgenual aspects), the striatum (including caudate nucleus and putamen), and the frontal operculum. An additional simple regression analysis showed that activity increases in the perigenual ACC and the striatum best predicted individual subjective pain decreases during positive compared to negative expectancy (Table 2 and Fig. 7).

Note, however, that stronger ACC activity during positive compared to negative expectancy and stronger hippocampus activity during negative compared to positive expectancy could be driven by increased activity of the ACC during positive expectancy, decreased ACC activity during negative expectancy, or both (and similarly so for the hippocampus result). To further unravel which condition is actually driving these effects, we extracted the parameter estimates from these areas identified to be associated with positive and negative activity and known from published literature to be relevant for driving placebo analgesia and nocebo hyperalgesia [subgenual ACC (sgACC) and hippocampus] (see Supplementary Material and fig. S3). This analysis revealed increased activity in the sgACC when analgesia is increased during positive expectancy and a deactivation of this region when analgesia is impaired during negative expectancy. In contrast, no response in the hippocampus was observed when remifentanil is applied in the no-expectation or the positive expectation condition, but a strong increase in activity occurs when analgesia is impaired during negative expectancy.

DISCUSSION

The present study explored how an individual's expectation of the effectiveness of a drug can influence analgesia during the application of the μ-opioid receptor agonist remifentanil. We found that positive treatment expectancies substantially enhanced, in fact doubled, the analgesic benefit of remifentanil. Negative treatment expectation interfered with the analgesic potential of remifentanil to the extent that the effect of this potent analgesic was completely abolished. These effects of subjective perception were paralleled by significant changes in neural responses to thermal noxious stimulation in core brain regions that are involved in the intensity coding of pain.

The first part of our study, which compared the analgesic efficacy of remifentanil, in terms of its net analgesic effect, without and with positive expectation, confirms previous behavioral observations that used hidden versus open application of analgesics. It shows that psychosocial factors, such as awareness of a drug being given, can considerably enhance the overall clinical response to a drug (*12*). This phenomenon is not restricted to analgesics, because similar effects have also been reported for treatments in other medical conditions (*13*). For instance, expectation increases the anxiolytic effects of diazepam in postoperative anxiety, the effect of deep brain stimulation of the subthalamic nucleus on motor performance in Parkinson's disease, and the subjective responses to psychotropic drugs such as Δ^9-tetrahydrocannabinol (*11*, *15*) or methylphenidate (*23*).

The hidden application of drugs is an artificial situation, mainly used in experimental studies. In medical practice, rather than having no expectations, as was true for one of our conditions, patients commonly have implicit or explicit expectations of their physician and their prescribed treatments. Therefore, we specifically tested these

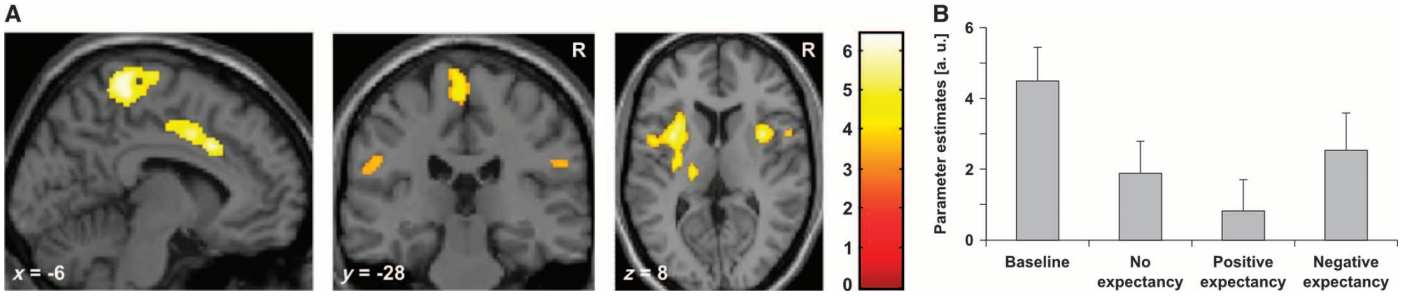

Fig. 5. Effect of expectancy modulation of opioid analgesia in the core regions of the pain neuromatrix. (**A**) Brain activity correlating with the changes in behavioral analgesia in the four experimental conditions. These correlations were identified with *z*-transformed mean ratings from the four experimental runs as contrast weights. The images are thresholded at $P < 0.001$ uncorrected. (**B**) Parameter estimates of pain-related BOLD responses averaged across the above shown brain regions for each of the experimental runs plotted for visualization purposes (extracted from a 6-mm sphere around the peak voxels of activation; for details, see Table 1). a.u., arbitrary units. Color bar indicates *t* score.

clinically relevant conditions of positive and negative expectancy. The negative treatment expectancy completely abolished the analgesic effect of a potent analgesic. Notably, this increase in pain behavior with negative expectancy that occurred after 60 min of being on an opioid is not due to opioid tolerance. This was confirmed by control experiment II (fig. S5), in which we demonstrated that the opioid regimen used in our study results in stable analgesia over the entire time course of an experiment when no expectancy manipulation is performed. This is further supported by the results from a recent healthy volunteer study that failed to demonstrate analgesic tolerance to remifentanil dosing regimens similar to that used in our study (*24*). The subjective effects that we observed (that is, changes in reported analgesia with different expectancies) are substantiated by significant changes of activation in core regions of the pain and opioid-sensitive brain networks, such as the thalamus, the MCC, and the primary somatosensory cortex. Activity in these brain areas has been consistently shown to be correlated with the intensity of nociceptive inputs and resultant pain perception (*18*, *19*), and therefore serves as an objective index of analgesic efficacy. These data provide strong objective evidence that context-related differences in reported analgesia, as observed here and in previous studies (*12*), are not the result of reporting bias.

fMRI revealed that the contextual manipulation of remifentanil analgesia is indeed accompanied by altered processing of ascending nociceptive input as reflected in activation differences in brain areas involved in pain processing and top-down pain modulation. These observations suggest that expectations about the effect of an active pharmacological substance selectively engage well-known mechanisms of descending facilitation and inhibition of pain, as has previously been reported for placebo and nocebo phenomena involving biologically inert compounds (*5*, *6*, *25*, *26*). Specifically, our data suggest that the descending pain control system plays a role in mediating the effect of positive treatment expectancy, because it was associated with activity in cingulo-frontal and subcortical brain areas that are known to contribute to both opioid and placebo analgesia. In contrast, negative expectancy that abolished the analgesic effect of the opioid was associated with reduced activity in the sgACC. This response pattern suggests that both positive and negative expectancy use a key component of the descending pain modulatory control system, but in opposite ways (fig. S3).

Further, we found that negative expectancy was selectively associated with increased activity in the hippocampus (fig. S3) and the medial prefrontal cortex. These brain areas have previously been implicated in the exacerbation of pain by mood and anxiety in patients as well as in healthy controls (*27*, *28*). Activity in medial frontal areas and hippocampus has also been observed in a recent study on the nocebo hyperalgesic effects during sham acupuncture (*29*). Negative treatment expectancy in our study produced a significant increase of anxiety. This is in line with the existing evidence that anxiety represents a powerful modulator in nocebo hyperalgesia (*30*), most likely via activation of the endogenous cholecystokinin (CCK) system (*8*). The CCK peptide is a known pronociceptive, anxiogenic neurotransmitter

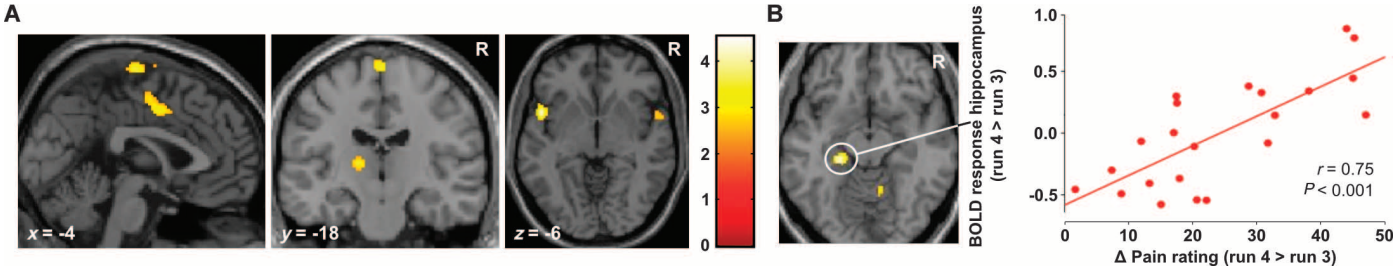

Fig. 6. Impaired analgesia during negative expectation is associated with hippocampal activity. (**A**) Pain-related BOLD responses during negative expectancy compared to positive expectancy (run 4 > run 3) overlaid on a T_1-weighted image. (**B**) Left: Simple linear regression analysis of the changes in BOLD response (parameter estimates run 4 > run 3, arbitrary units) with the individual difference in pain rating between negative and positive treatment expectancy. The images are thresholded at $P < 0.005$ uncorrected for visualization purposes. Color bar indicates *t* score. Right: Scatter plot of the individual behavioral effect between negative and positive expectancy (*x* axis) and the parameter estimates of the left hippocampus in the simple regression analysis (*y* axis). Parameter estimates are derived from a 6-mm sphere around the peak voxel of the regression analysis (–22, –28, –12; $t = 5.1$).

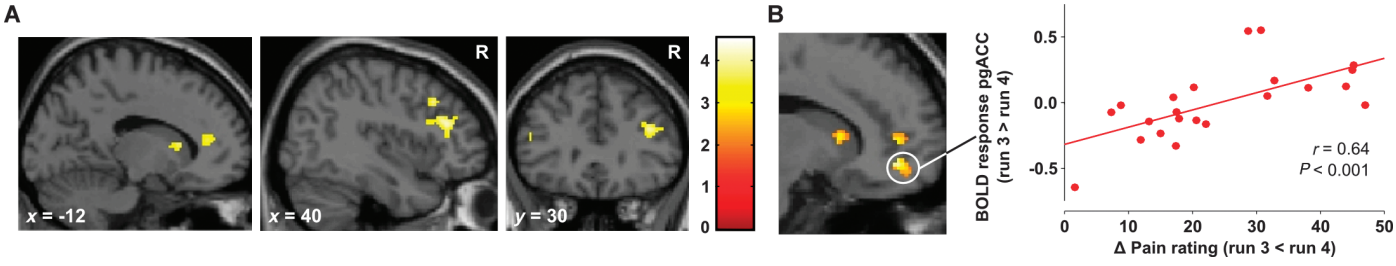

Fig. 7. Recruitment of the descending pain modulatory system with positive expectancy. (**A**) Pain-related BOLD responses during positive expectancy compared to negative expectancy (run 3 > run 4) overlaid on a T_1-weighted image. (**B**) Left: Simple linear regression analysis of the changes in BOLD response (run 3 > run 4) with the individual behavioral effect of positive versus negative treatment expectancy. The images are thresholded at $P < 0.005$ uncorrected for visualization purposes. Color bar indicates *t* score. Right: Scatter plot of the individual difference in pain rating between positive and negative expectancy (*x* axis) and the parameter estimates (arbitrary units) of the perigenual ACC (pgACC) in the simple regression analysis (*y* axis). Parameter estimates are derived from a 6-mm sphere around the peak voxel of the regression analysis (14, 48, –8 for *x*, *y*, and *z*; $t = 3.8$).

found in some of the key structures of the descending pain modulatory system, such as the PAG (*31*).

Our experimental data from healthy volunteers have implications for clinical practice. Even though our BOLD methodology does not allow for detecting interactions at the receptor/drug level, our data objectively demonstrate that pharmacological and psychological factors, such as an individual's expectation, ultimately converge at the neuronal level and can substantially improve or abolish the net analgesic effect of a potent analgesic. Similar interactions of pharmacodynamics and psychological effects on regulatory brain mechanisms have been reported for the administration of methylphenidate in cocaine-addicted patients (*23*). A crucial question is how these experimental data translate to clinical pain states. There are several reasons to believe that the present experimental results underestimate rather than overestimate related effects in clinical practice. First, we used a fixed order of experimental conditions, where negative expectancy was always induced after a positive experience in the open application condition, which reduces rather than amplifies the effect induced by the negative expectations. Second, the negative treatment expectancy in our study was induced by only a short expectancy manipulation period (hours) when compared to the sometimes year-long experience of failure of analgesic treatments observed in chronic pain patients. Finally, tonic and clinically relevant pain is even more susceptible to modulation by psychological factors compared to phasic experimental pain, as used in our study (*32*, *33*).

Table 2. The opposing effects of positive and negative expectation on opioid analgesia. BOLD responses to identical pain stimuli during the negative expectancy run compared to the positive expectancy run. Coordinates are denoted by *x*, *y*, *z* in millimeters (MNI space), and strength of activation is expressed in *t* scores (df = 63). All *P*s < 0.05 corrected (*), using SVC as indicated in Supplementary Methods, or 0.001 uncorrected, except (+) = *P* < 0.005 uncorrected. rACC, rostral ACC; pgACC, perigenual ACC; sgACC, subgenual ACC; DLPFC, dorsolateral prefrontal cortex; MCC, midcingulate cortex; MPFC, medial prefrontal cortex; PAG, periaqueductal gray; VLPFC, ventrolateral prefrontal cortex.

Region	Coordinate of peak voxel		Voxel level (T)
	R	L	R/L
Increased activity in pain-related areas MPFC and hippocampus with negative treatment expectancy (run 4 > run 3)			
SI		−10, −48, 76	/4.5*
MCC	2, −2, 44		3.6/
Insula	48, 18, −12	−50, 10, −6	3.3^{+}/4.4*
Thalamus		−16, −18, 8	/3.5*
Cerebellum	46, −60, −26		4.0/
Hippocampus	26, −22, −14	−18, −24, −14	3.1^{+}/3.7*
MPFC	2, 60, 20		3.0^{+}/
Correlation with the individual behavioral effect [regions whose activity for contrast (run 4 > run 3) correlates with the individual increase in pain rating (run 4 > run 3)]			
Hippocampus		−22, −28, −12	/5.1*
MCC	4, −20, 36	−4, −16, 44	4.3*/3.6
MPFC	8, 54, 38		3.1^{+}/
Increased activity in the endogenous pain modulatory system with positive treatment expectancy (run 3 > run 4)			
DLPFC	38, 22, 38		4.8*/
VLPFC	40, 34, 22		3.9*/
Precentral gyrus	32,−22, 62		4.0/
rACC		−16, 38, 12	/4.0*
sgACC	6, 16, −14		4.2*/
Striatum, caudate nucleus	16, 20, 8	−16, 16, 8	2.8^{+}/3.7*
Striatum, putamen	32, −2, 6		3.7*/
Frontal operculum		−52, 18, 12	/3.9*
Correlation with individual behavioral effect [regions whose activity for contrast (run 3 > run 4) correlates with the individual decrease in pain rating (run 3 < run 4)]			
pgACC	14, 48, −8		3.8*/
Striatum, caudate nucleus	14, 16, 6		3.0 $^{+}$/
Frontal operculum	44, 32, −2		3.9/

Treatment expectations are shaped by various factors, including previous experiences with physicians and treatments. Particularly in patients with chronic diseases, treatments often fail repeatedly. Frustration inevitably mounts and may result in negative expectancies for future treatments. Furthermore, the negative mood states that occur in patients with chronic disease (*34*) themselves may generate negative treatment expectations and increased anxiety. In these situations, drugs with biologically plausible intrinsic actions compete with the negative treatment expectancies of the patient that directly activate similar target brain regions, and as such could modulate or, in the worst case, completely abolish the drug's effects and clinical outcome. The underestimation of the influence that psychological states have on drug pharmacodynamics might therefore, inadvertently, contribute to the frequent failure of clinical translation of drugs that show target engagement in preclinical studies, especially when drugs are developed for the treatment of chronic illness.

Treatment expectations are, however, malleable and can be brought under direct behavioral control by instruction. Influencing beliefs about outcome by the careful use of language and provision of appropriate information regarding the expected drug effect should be considered as an important feature of every pharmacological treatment. Indeed, this is already done by some physicians. However, the observation that, in the United States, 50% of patients leave after an office visit without an adequate understanding of what the physician has told them (*35*) highlights a need to improve this element of the patient-physician interaction if we are to improve treatment outcomes.

From a clinical trial perspective, rather than seeking to control for psychological components, trial designs could be developed that aim to maximize the effects of therapeutic agents by integrating the effects of expectation and active treatment. For example, understanding and creating disease- and drug-specific therapeutic contexts that optimally enhance the pharmacological effects of the drug could be beneficial. The proof of a neurobiological basis of expectancy effects on drug efficacy opens a new avenue of research, namely, a detailed understanding of drug, personality, therapeutic context, and disease-specific interactions between the pharmacological agents and cognitively triggered endogenous neurobiological mechanisms (*36*). Future studies, involving different methodologies and designs, should be performed to unravel the effects of treatment expectations on drug action at a receptor/molecular level and to determine whether the

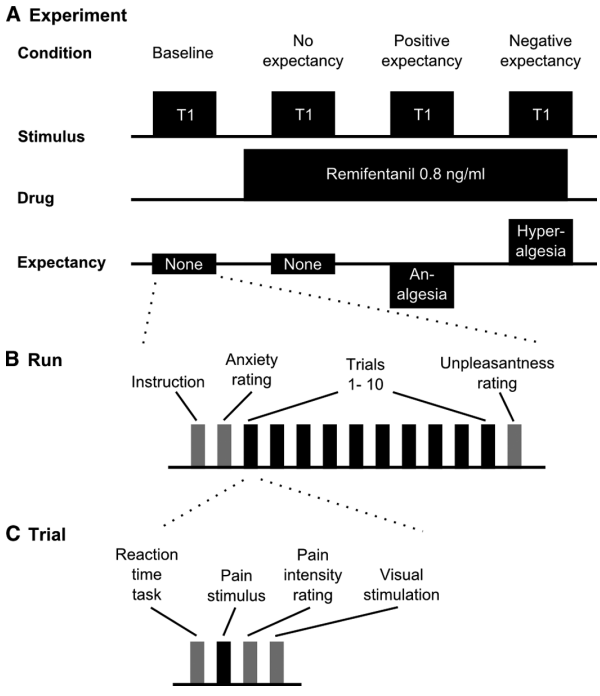

Fig. 8. Experimental design (fMRI). (**A**) The main experimental paradigm performed with fMRI consisted of four runs of thermal painful stimulation. The first run was completed with a saline infusion only. Thirty minutes before the second run, a target-controlled remifentanil infusion (effect site concentration, 0.8 ng/ml) was started and continued throughout runs 2 to 4. In runs 2 to 4, the analgesic effect of a constant dose of remifentanil was studied in three different contextual conditions: without expectancy of analgesia (no expectancy), with positive expectancy (expect analgesia), and with a negative expectancy (expect hyperalgesia). The same (individually predetermined) thermal pain intensity (T1) was used throughout all runs (for details, see main text). (**B**) Each of the four runs included 10 identical pain trials [see (C)]. At the beginning of each run, participants were instructed about the particular experimental condition and participants rated their current anxiety levels. At the end of each run, participants rated the overall unpleasantness of the 10 painful stimuli. For runs 3 and 4, the participant was also asked to rate the expected change in their pain sensations before the third (remifentanil) and fourth (remifentanil stopped) runs of thermal stimulation on a VAS. (**C**) Each trial included a pain anticipation phase, painful thermal stimulation, pain rating, a simple reaction time task, and a visual control stimulus. During the trial, the participant was asked to fixate on a cross (initially colored gray), which was presented in the middle of the projection screen in the scanner. The color of the fixation cross was used to cue to different events during the trial. A color change from gray to yellow signaled the start of the trial. This began with a simple reaction time task during which the participant was asked to indicate as quickly as possible the position of a white square that appeared either at the right- or at the left-hand side of the screen, by pressing the corresponding button on a computer mouse, placed in the right hand. Upon completion of the reaction time task, the color of the fixation cross switched to red to signal the impending painful stimulus. This anticipatory phase was 4 to 8 s long. Then, a 6-s painful thermal stimulus of a fixed intensity (as determined in the calibration session) was delivered. Four to 8 s after thermal stimulation, the participant rated the intensity of pain on the VAS (mean duration 3.5 s). After 7 to 10 s, the subject then passively viewed a flickering visual checkerboard (frequency, 4 Hz), which lasted 1.5 s.

effects of expectation and drug effect combine in an additive or interactive manner, as this cannot be answered with the current study design.

Our results suggest that a consideration of the contribution of negative experience and expectancy to analgesic efficacy is necessary, but the conclusions may also apply to any pharmacological treatment, particularly in chronic disease. A new and systematic appreciation of the role of individual differences (genetic, psychological, and neurological) among humans is ushering in the exciting possibility of personalized medicine. Understanding and controlling the psychological context in which medicines are delivered will be an important part of making this move from the general to the personal successful.

MATERIALS AND METHODS

Participants

Twenty-two healthy volunteers (7 female and 15 male; all right-handed; mean age, 28 years; range, 21 to 40 years) completed the study. All participants had normal heat pain thresholds at the site where noxious stimuli were applied and were not taking any medication. There was no history of neurological or psychiatric disease. None of the participants suffered from clinical pain, and all were naïve to opioids. The study was approved by the local ethics committee (Oxfordshire Research Ethics Committee B) and conducted in conformity with the Declaration of Helsinki, and written informed consent was obtained from all subjects. The participants were recruited with the understanding that the study aimed to investigate the brain mechanisms responsible for interindividual differences in the response to opioids. They were also informed that remifentanil is a widely used opioid that relieves pain when infused intravenously, but can worsen pain when the infusion ceases (*37*).

Study design

The study comprised two sessions: one introductory session and one main experimental session including fMRI. The two experimental sessions were separated by at least 24 hours. The study procedures followed well-established paradigms of placebo analgesia including expectation and conditioning components (*33*, *38*–*40*).

Introductory session. This behavioral session was used to familiarize the participants with the experimental procedures (for example, pain stimuli, the rating procedures, and physiological monitoring), to ensure that the participants tolerated intravenous remifentanil, and to introduce the experimental paradigm used during the main experimental session. It also included a conditioning procedure to induce positive and negative treatment expectations (see Supplementary Methods and fig. S1 for details).

Main experimental session. The main experimental session consisted of four runs of identical thermal stimulation, each including 10 thermal pain stimuli and lasting ~10 min (Fig. 8). After a baseline run performed with a saline infusion only, the analgesic effect of remifentanil was assessed in three different conditions: (i) no expectancy, (ii) with positive expectancy, and (iii) with negative expectancy.

The participants were welcomed and an anesthetist checked that the participant had no contraindication to any of the procedures involved. After insertion of an intravenous cannula for drug administration, the participant was then positioned in the MR scanner and familiarized with the experimental setup in the MR environment. A contact heat stimulus delivery thermode [30 × 30 mm ATS (Advanced Thermal Stimulator) thermode, Pathway System, Medoc] was attached

to the lateral aspect of the right mid-calf. For each participant, the temperature of the thermode was adjusted to produce a pain intensity rating of 70 on a VAS, where 0 corresponds to "no pain" and 100 to "unbearable pain." This temperature was delivered during all runs.

The first run was performed with a saline infusion only. Unbeknown to the participant, the remifentanil infusion was started after the first run, so that in the second run, the analgesic effect of remifentanil could be assessed without any treatment expectation. To distract from potentially noticeable psychotropic effects with the rising concentrations of remifentanil, we performed a structural brain scan (duration, 15 min) after starting the remifentanil infusion. The participant was told that the imaging sequence would cause "vibrations that may evoke a sensation of slight disorientation in some participants." The second run, which constitutes the "no expectancy" run, followed the structural scan and occurred after remifentanil had been infused for 30 min, which ensured that plasma and effect site concentrations were at equilibrium at 0.8 ng/ml. Pilot data further indicate that subjective reports of analgesia were stable during that period (see control experiment II, Supplementary Methods and Results, and fig. S5). After this run, the participant was told that the infusion "would be now started by the anesthetist" and the third run, representing the "positive expectancy" run, was started 10 min later. Upon its completion, the participant was told that "the infusion would now be stopped to investigate the possible increase in pain after ceasing the opioid infusion." However, in reality, the infusion was continued throughout the fourth run. This fourth run represents the "negative expectancy" run.

Each run lasted about 10 min and consisted of 10 identical pain trials. Each trial included a painful thermal stimulus (~1.5-s ramp-up, 6-s plateau, ~1.5-s ramp-down) applied to the right mid-calf by the contact heat stimulus delivery thermode and was followed by a pain intensity rating performed on a VAS (100 parts; endpoints labeled with no pain and unbearable pain). Participants also rated their anxiety levels at the beginning of each run and the overall unpleasantness of the 10 painful stimuli at the end of each run on a VAS (100 parts; endpoints "not anxious" and "extremely anxious" for anxiety and endpoints "not unpleasant" and "extremely unpleasant" for unpleasantness). In addition, the participants rated the expected change in their pain sensations immediately before the positive and negative expectancy runs on a VAS, where 0 corresponds to "no change" and 100 to "complete pain relief" for the positive expectancy run and to "worst pain" in the negative expectancy run. To minimize the effects of habituation or sensitization during the course of the experiment, we slightly changed the site of thermal stimulation along the right mid-calf after each of the four runs. As confirmed by pilot data, this regimen results in stable pain ratings across trials and sessions if no pharmacological or expectancy modulation is performed (see control experiment I, Supplementary Methods and Results, and fig. S5). After the four runs, the intravenous cannula was removed and participants were accompanied to a room next to the scanner. Here, the participants' confidence in the actual experimental conditions was evaluated with a post hoc questionnaire designed to assess potential unblinding (for details, see Supplementary Methods and Results). At the end of the study, the participants were fully debriefed regarding the actual experimental procedures.

Drug administration and physiological monitoring

An anesthetist monitored the participants during the experiment. In the main experimental session, an estimated effect site (within the brain) concentration of 0.8 ng/ml was achieved with a target-controlled infusion pump (Graseby 3500 TCI incorporating Diprifusor; SIMS Graseby). It delivered the infusion rate based on a pharmacological model of remifentanil that included the participants' weight, height, and gender (*41*, *42*). The participants' heart rate, peripheral blood oxygen saturation (Spo_2), respiratory rate, and end-tidal CO_2 partial pressure (P_{ETCO_2}) were recorded (9500 Multigas Monitor, Wardray Premise). To prevent hypoxemia as a result of opioid-induced hypoventilation, we delivered oxygen (1 liter/min) via nasal prongs (Salter Labs) during all runs. For a detailed description and pilot data supporting the choice of regimen, see Supplementary Methods and Results.

Control experiments

Two control experiments were performed to confirm that expectation-dependent changes in pain perception are not attributable to sensitization or habituation phenomena or time-dependent changes of opioid analgesia (for details and results, see Supplementary Methods and Results).

fMRI data acquisition

fMRI data using T_2^*-weighted echo-planar images covering the brain and brainstem were acquired throughout each of the four runs on a 3-T system (Varian, Siemens) equipped with a four-channel head coil using standard techniques (for details, see Supplementary Methods).

Data analysis and statistics—behavior

Behavioral effects pertain to the main experimental session and were analyzed in SPSS Statistics 17 software package. The normal distribution of the data was tested with the Kolmogorov-Smirnov test.

Pain ratings, anxiety ratings, and the physiological data of the four experimental conditions were analyzed with repeated-measures ANOVAs. In case of significant F tests, these were followed by post hoc paired t tests with Bonferroni correction for multiple comparisons. Here, the intrinsic analgesic effect of remifentanil was assessed by comparing the no expectancy run and the baseline run. The hypothesized additional analgesia because of positive treatment expectancy was determined by comparing the no expectancy and the positive expectancy runs. The effect of negative treatment expectancy was assessed by the comparison of the positive expectancy and the negative expectancy runs.

Pearson correlation coefficients were calculated to examine the relationship between the different experimental effects. The level of significance was set at $P < 0.05$. Unless indicated otherwise, results are presented as means ± SEM.

Data analysis—fMRI

Data processing and statistical analyses were carried out with statistical parametric mapping (SPM5, Wellcome Trust Centre for Neuroimaging) involving standard approaches for the analysis of functional imaging, which are described in full detail in Supplementary Methods. In short, these analyses identified pain-related BOLD responses, which reflect neuronal activity, and compare these between the four different experimental conditions (baseline, no expectancy, positive expectancy, and negative expectancy) on the group level. Additional simple linear regression analyses as implemented in SPM5 were performed to identify context-specific correlations of individual BOLD responses and behavioral effects (for example, changes in analgesia).

Note that the design used in this study does not allow us to formally test for statistical interaction effects (that is, dissecting additive from interactive effects of expectation and drug effect).

SUPPLEMENTARY MATERIAL

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Methods
Results
Fig. S1. Experimental design during the introductory session.
Fig. S2. The effect of expectancy modulation of opioid analgesia in the core regions of the pain neuromatrix.
Fig. S3. Brain areas mediating the effects of positive and negative expectancy.
Fig. S4. Control experiment I—exclusion of habituation or sensitization effects.
Fig. S5. Control experiment II—the natural time course of remifentanil analgesia without expectancy manipulation.
Fig. S6. Analysis of the time course of changes in analgesia during the fMRI experiment.
Table S1. Effect of painful thermal stimulation.
Table S2. Intrinsic effect of remifentanil on painful thermal stimulation.
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